Immune-Based Therapy Under Evaluation for Treatment of COVID-19

Last Updated: July 17, 2020

Given the hyperactive inflammatory effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), agents that modulate the immune response are being explored as adjunctive treatments for the management of moderate to critical COVID-19.[1] These agents include human blood-derived products and immunomodulatory therapies.

Some human blood-derived products are obtained from individuals who have recovered from SARS-CoV-2 infection (e.g., convalescent plasma, immunoglobulin products).[2,3] These heterogenous products are postulated to have either direct antiviral properties, such as with convalescent plasma, and/or immunomodulatory effects like those noted with mesenchymal stem cells.[4] Additionally, neutralizing monoclonal antibodies directed against SARS-CoV-2 have been developed and are under investigation in clinical trials.[5]

Other agents in this group include therapeutics currently approved for the treatment of other immune and/or inflammatory syndromes. These agents include corticosteroids (e.g., glucocorticoids),[6] which as a class possess a broad array of mechanisms to abrogate systemic inflammation, and more targeted anti-inflammatory treatments such as interleukin inhibitors,[7,8] interferons,[9] kinase inhibitors,[10] and others.

In the following sections of the COVID-19 Treatment Guidelines, different blood-derived products and immunomodulators under investigation for the management of COVID-19 are discussed. Items discussed include the proposed rationale for use of these therapies, the clinical safety and efficacy data to date, and the COVID-19 Treatment Guidelines Panel's recommendations for their use.

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Blood-Derived Products Under Evaluation for the Treatment of COVID-19

Last Updated: July 17, 2020

Summary Recommendations

• There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19:
  • **COVID-19 convalescent plasma**
  • **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins**
• The Panel **recommends against** the use of the following blood-derived products for the treatment of COVID-19, except in a clinical trial:
  • **Mesenchymal stem cells (AII)**
  • **Non-SARS-CoV-2-specific intravenous immunoglobulins (IVIG) (AIII)**. This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Convalescent Plasma

Last Updated: July 17, 2020

Recommendation:

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of **COVID-19 convalescent plasma** for the treatment of COVID-19.

Rationale for Recommendation

Thousands of patients in the United States have received COVID-19 convalescent plasma through clinical trials, expanded access treatment trials, and single-patient Emergency Investigational New Drug (EIND) applications. However, the standards and methods for screening donated plasma for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binding and neutralizing antibodies have not been established. The variability in SARS-CoV-2 antibody levels in donor plasma may have an impact on the efficacy of COVID-19 convalescent plasma products. Clinical data are currently insufficient to evaluate the efficacy of convalescent plasma for the treatment of COVID-19. Safety data from a large, multicenter, expanded access program indicated that uncommon (i.e., in <1% of transfusions) but serious risks of convalescent plasma may include transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), allergic reactions, and death.[1] Another theoretical risk is potential for antibody-dependent enhancement (ADE) of infection.

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that may help suppress the virus and modify the inflammatory response.[2]

Clinical Data to Date

Open-Label, Randomized Clinical Trial of Convalescent Plasma in 103 Hospitalized Patients With Severe or Life-Threatening COVID-19

This open-label, randomized clinical trial of convalescent plasma versus standard of care for patients with severe or life-threatening laboratory-confirmed COVID-19 was conducted in seven medical centers in Wuhan, China, from February 14 to April 1, 2020. The primary outcome was time to clinical improvement within 28 days, which was defined as patient discharged alive or a two-point reduction on a six-point disease severity scale. Only plasma units with a SARS-CoV-2 viral spike-receptor binding domain-specific IgG titer of at least 1:640 were transfused. The median dose of ABO-compatible, transfused convalescent plasma was 200 mL. The time from symptom onset to study randomization was 27 days in the treatment group and 30 days in the control group.[3]

Due to control of the COVID-19 outbreak in Wuhan, the trial was terminated early after 103 of the planned 200 patients were enrolled. Among the enrolled patients, 45 had severe disease and 58 had life-threatening disease. Baseline severity scores and use of concomitant therapies were similar between the treatment and control groups. Although the groups were well-balanced by age (with a median age of 70 years in the treatment group vs. 69 years in the control group), the proportion of men in the control group (65%) was greater than in the convalescent plasma group (52%). There was no significant difference between the treatment and control groups in the primary outcome of time to clinical improvement within 28 days (hazard ratio 1.40; 95% confidence interval [CI], 0.79–2.49; *P* = 0.26). Among those with severe disease, 91% of the convalescent plasma recipients and 68% of the control patients improved by Day 28 (difference 23%; odds ratio [OR] 1.34; 95% CI, 0. 98–1.83; *P*

= 0.07). Among those with life-threatening disease, 21% of patients in the treatment group and 24% in the control group improved (difference -3.4%; OR 0.86; 95% CI, 0.33–2.24; $P = 0.75$). There was no significant difference in mortality between the groups (16% vs. 24% for the treatment and control groups, respectively; OR 0.65; 95% CI, 0.29–1.46; $P = 0.30$). At 24, 48, and 72 hours, the rates of negative SARS-CoV-2 viral polymerase chain reaction were significantly higher in the convalescent plasma group than in the control group (45% vs. 15%, respectively, at 24 hours, $P = 0.003$; 68% vs. 33%, respectively, at 48 hours, $P = 0.001$; and 87% vs. 38%, respectively, at 72 hours, $P < 0.001$). Two transfusion-related events were reported, including one severe event; both events resolved with supportive care.

Limitations

The limitations of this study include that it was not blind and that, on average, the convalescent plasma was administered approximately 1 month into the disease course. In addition, the study was terminated early, and thus the sample size was insufficient to detect smaller but clinically meaningful differences in clinical outcomes.

Safety Analysis of the First Consecutive 20,000 Patients to Receive Open-Label COVID-19 Convalescent Plasma Through a National Expanded Access Program

The Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19 program is an ongoing, open-label, nonrandomized protocol primarily designed to provide adult patients who have severe or life-threatening (critical) COVID-19 with access to convalescent plasma, which is an investigational product in the United States. Secondary objectives are to obtain data on the safety of the intervention. The program is sponsored by the Mayo Clinic and includes a diverse range of clinical sites. Criteria for plasma donors include documented COVID-19, with complete resolution of symptoms for ≥14 days before donation, and either no history of pregnancy or a negative human leukocyte antigen test after a donor's most recent pregnancy. SARS-CoV-2 antibody testing of plasma donors and assessment of SARS-CoV-2 neutralization potential are not mandated. Patients are transfused with 1 or 2 units (200–500 mL) of convalescent plasma. ABO-compatible plasma is used preferentially, but in the absence of ABO-compatible plasma, patients may receive either Group A plasma or low anti-A titer Group O plasma, as available. The main outcomes for the safety analysis are serious adverse events (SAEs), including death; SAEs are reported at 4 hours and at 7 days after transfusion, or as they occur.[4]

The safety analysis describes the first 20,000 plasma recipients, enrolled between April 3 and June 2, 2020. One-third of the participants were aged ≥70 years, 60% were male, and 71% had severe or life-threatening COVID-19. Twenty percent of the participants were African American, 35% were Hispanic/Latino, and 5% were Asian. SAEs within 4 hours of transfusion were reported in 146 (<1%) patients and included 63 deaths. Among the deaths, 13 were determined to be possibly or probably related to the convalescent plasma treatment. The 83 nonfatal SAEs included 37 TACO events, 20 TRALI events, and 26 severe allergic reactions. Life-threatening cardiac events and thrombotic events reported up to 7 days after transfusion included 87 thrombotic/thromboembolic complications, 406 sustained hypotension events, and 643 cardiac events. The overall mortality rate was 8.6% at 7 days. In this study, COVID-19 convalescent plasma therapy was associated with a low incidence (<1%) of serious transfusion-related events.

Limitations

The study design, which does not include a control arm, precludes an assessment of efficacy or the occurrence of ADE of COVID-19.

Retrospective, Single-Center, Case-Control Study Evaluating Convalescent Plasma Plus Standard of Care Versus Standard of Care Without Convalescent Plasma

This study has not been peer reviewed.

This case-control study reports clinical outcomes among 39 consecutive patients who received COVID-19 convalescent plasma through the Food and Drug Administration (FDA) single-patient EIND program while hospitalized at Mount Sinai Hospital in New York City between March 24, 2020, and April 8, 2020. Recipients were transfused with 2 units of ABO-compatible convalescent plasma from donors with a SARS-CoV-2 anti-spike antibody titer of 1:320 dilution. The control group (n = 156) was identified retrospectively from the hospital's electronic health records database. The control patients were hospitalized during the same period as the treated patients, had confirmed COVID-19, did not receive convalescent plasma, and were matched 4:1 to convalescent plasma recipients using propensity scores to correct for measured confounders.[5]

The mean age of the convalescent plasma recipients was 55 years, and 64% of the recipients were male. At the time of transfusion, 34 recipients (87%) required supplemental oxygen (noninvasive), and four recipients (10%) were mechanically ventilated. By Day 14, the clinical condition had worsened in 18% of the convalescent plasma patients and 24% of the control patients ($P = 0.17$). As of May 1, 2020, 13% of the plasma recipients and 24% of the matched control patients had died ($P = 0.04$, log-rank test), and 72% and 67% of the transfused patients and control patients, respectively, had been discharged from the hospital.

Limitations

The study's lack of randomization and the potential for unmeasured patient selection bias limit interpretation of the study results.

Other smaller, uncontrolled case series that describe clinical outcomes in COVID-19 patients have been reported and also suggest that SAEs are uncommon following COVID-19 convalescent plasma treatment.[2,6-11]

Clinical Data for Other Viral Infections

The use of convalescent plasma has been evaluated for other viral diseases, such as SARS, with some suggestion of potential benefit.[12-14] However, no convalescent blood products are currently licensed by the FDA.

Clinical Trials

Randomized clinical trials to evaluate convalescent plasma for the treatment of COVID-19 are underway; a list is available at *ClinicalTrials.gov*.

Drug Availability

The FDA has provided recommendations for the use of COVID-19 convalescent plasma through EIND applications for individual patients and traditional or expanded access IND applications. The FDA has also approved a national expanded access program for the use of convalescent plasma for the treatment of patients with COVID-19. Clinicians can refer to the National COVID-19 Convalescent Plasma Project website for more information on that specific program and other trials evaluating convalescent plasma. People who have fully recovered from COVID-19 for ≥2 weeks and who are interested in donating plasma can contact their local blood donor or plasma collection center or refer to the FDA's Donate COVID-19 Plasma website.

Adverse Effects

The risks associated with convalescent plasma transfusion include TRALI, TACO, and allergic transfusion reactions.[8,15] Rare complications include the transmission of infectious pathogens and red cell alloimmunization. There is a theoretical risk of antibody-mediated enhancement of infection.

Considerations in Pregnancy

Several ongoing clinical trials evaluating COVID-19 convalescent plasma include pregnant women.

Considerations in Children

Clinical trials of COVID-19 convalescent plasma in children are ongoing.

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Immunoglobulins: SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins** for the treatment of COVID-19.

Rationale

Currently, there are no clinical data on the use of SARS-CoV-2 immunoglobulins. Trials evaluating SARS-CoV-2 immunoglobulins are in development but not yet active and enrolling participants.

Proposed Mechanism of Action and Rationale for Use in Patients with COVID-19

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response. The use of virus-specific immunoglobulins for other viral infections (e.g., cytomegalovirus [CMV] immunoglobulin for the prevention of post-transplant CMV infection and varicella zoster immunoglobulin for postexposure prophylaxis of varicella in individuals at high-risk) has proven to be safe and effective; however, there are currently no clinical data on the use of such products for COVID-19. Potential risks may include transfusion reactions. Theoretical risks may include antibody-dependent enhancement of infection.

Clinical Data

There are no clinical data on the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. Similarly, there are no clinical data on use of specific immunoglobulin or hyperimmunoglobulin products in patients with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).

Considerations in Pregnancy

Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent varicella zoster virus (VZV) and rabies and have also been used in clinical trials of therapies for congenital CMV infection.

Considerations in Children

Hyperimmunoglobulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus, and CMV; efficacy data on their use for other respiratory viruses is limited.

Immunoglobulins: Non-SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of non-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific **intravenous immunoglobulin (IVIG)** for the treatment of COVID-19, except in a clinical trial **(AIII)**. This recommendation **should not preclude** the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Rationale for Recommendation

Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, it is unknown whether products derived from the plasma of donors without confirmed SARS-CoV-2 infection contain high titer of SARS-CoV-2 neutralizing antibodies. Furthermore, although other blood components in IVIG may have general immunomodulatory effects, it is unclear whether these theoretical effects will benefit patients with COVID-19.

Clinical Data for COVID-19

This study has not been peer reviewed.

A retrospective, non-randomized cohort study of IVIG for the treatment of COVID-19 was conducted across eight treatment centers in China between December 2019 and March 2020. The study showed no difference in 28-day or 60-day mortality between 174 patients who received IVIG and 151 patients who did not receive IVIG.[1] More patients in the IVIG group had severe disease at study entry (71 patients [41%] with critical status in the IVIG group vs. 32 patients [21%] in the non-IVIG group). The median hospital stay was longer in the IVIG group (24 days) than in the non-IVIG group (16 days), and the median duration of disease was also longer (31 days in the IVIG group vs. 23 days in the non-IVIG group). A subgroup analysis that was limited to the critically ill patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days.

The results of this study are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive either IVIG or no IVIG, and the patients in the IVIG group were older and more likely to have coronary heart disease than those in the non-IVG group. In addition, the IVIG group had a higher proportion of patients with severe COVID-19 disease at study entry. Patients in both groups also received many concomitant therapies for COVID-19.

Considerations in Pregnancy

IVIG is commonly used in pregnancy for other indications such as immune thrombocytopenia with an acceptable safety profile.[2,3]

Considerations in Children

IVIG has been widely used in children for the treatment of a number of conditions. including Kawasaki disease, and is generally safe.[4] IVIG has been used in pediatric patients with COVID-19 and multiorgan inflammatory syndrome in children (MIS-C), especially those with a Kawasaki disease-like presentation, but the efficacy of IVIG in the management of MIS-C is still under investigation.

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Mesenchymal Stem Cells

Last Updated: July 17, 2020

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of **mesenchymal stem cells (MSCs)** for the treatment of COVID-19, except in a clinical trial **(AII)**.

Rationale for Recommendation

MSCs are investigational products that have been studied extensively for broad clinical applications in regenerative medicine[1] and for their immunomodulatory properties.[2] No MSCs are approved by the Food and Drug Administration (FDA) for the treatment of COVID-19. There are insufficient data to assess use of MSCs for the treatment of COVID-19.

The FDA has recently issued several warnings about patients being potentially vulnerable to stem cell treatments that are illegal and potentially harmful.[3] Several cord blood-derived products are currently licensed by the FDA for indications such as the treatment of cancer (e.g., stem cell transplant) or rare genetic diseases, and as scaffolding for cartilage defects and wound beds. None of these products are approved for the treatment of COVID-19 or any other viral disease.[4] In the United States, MSCs **should not be used** for the treatment of COVID-19 outside of an FDA-approved clinical trial, expanded access programs, or an Emergency Investigational New Drug application **(AII)**.

Rationale for Use in COVID-19

MSCs are multipotent adult stem cells that are present in most human tissues, including the umbilical cord. MSCs can self-renew by dividing and can differentiate into multiple types of tissues, including osteoblasts, chondroblasts, adipocytes, hepatocytes, and others, which has led to a robust clinical research agenda in regenerative medicine. It is hypothesized that MSCs could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Furthermore, MSCs lack the angiotensin-converting enzyme 2 receptor that SARS-COV-2 uses for viral entry into cells; therefore, MSCs are resistant to infection.[5,6]

Clinical Data

Data supporting the use of MSCs in patients with viral infections, including COVID-19, are limited to case reports and small, open-label studies.

Clinical Data for COVID-19

- A pilot study of intravenous MSC transplantation in China enrolled 10 patients with confirmed COVID-19 categorized according to the National Health Commission of China criteria as critical, severe, or common type. Seven patients (one with critical illness, four with severe illness, and two with common-type illness) received MSCs; three patients with severe illness received placebo. All seven patients who received MSCs recovered. Among the three severely ill control patients, one died, one developed acute respiratory distress syndrome (ARDS), and one remained stable with severe disease.[7]

Clinical Data for Other Viral Infections

- In an open-label study of MSCs for the treatment of H7N9 influenza in China, 17 patients received MSC treatment plus standard of care, and 44 patients received standard of care only. In the MSC

group, three patients (17.6%) died; in the control group, 24 patients (54.5%) died. The 5-year follow-up was limited to five patients in the MSC group. No safety concerns were identified.[8]

Clinical Trials

See *ClinicalTrials.gov* for a list of clinical trials evaluating MSCs for the treatment of COVID-19 and COVID-19-related ARDS that are underway and recruiting participants.

Adverse Effects

Risks associated with MSC transfusion appear to be uncommon. The potential risks include failure of the cells to work as expected, potential for MSCs to multiply or change into inappropriate cell types, product contamination, growth of tumors, infections, thrombus formation, and administration site reactions.[9]

Considerations in Pregnancy

There are insufficient data to assess the risk of MSC use during pregnancy.

Considerations in Children

There are insufficient data on the efficacy and safety of MSC use in children.

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Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: July 17, 2020

Summary Recommendations
Dexamethasone • The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** (at a dose of 6 mg per day for up to 10 days) for the treatment of COVID-19 in patients who are mechanically ventilated **(AI)** and in patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**. • The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**. **Other Immunomodulators** There are insufficient data for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19: • **Interleukin-1 inhibitors** (e.g., **anakinra**) • **Interleukin-6 inhibitors** (e.g., **sarilumab**, **siltuximab**, **tocilizumab**) • **Interferon-beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19. The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial: • **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 **(AIII)** • **Bruton's tyrosine kinase inhibitors** (e.g., **acalabrutinib**, **ibrutinib**, **zanubrutinib**) and **Janus kinase inhibitors** (e.g., **baricitinib**, **ruxolitinib**, **tofacitinib**) **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Corticosteroids (Including Dexamethasone)

Last Updated: July 17, 2020

Recommendation for Patients with COVID-19

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** (at a dose of 6 mg per day for up to 10 days) for the treatment of COVID-19 in patients who are mechanically ventilated **(AI)** and in patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**.

Rationale

A preliminary, unpublished analysis from a multicenter, randomized, open-label trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) in hospitalized patients with COVID-19 showed that patients who were randomized to receive dexamethasone had a lower mortality rate than those who received standard of care. This benefit was observed in patients who required supplemental oxygen at enrollment. No benefit of dexamethasone was seen in patients who did not require supplemental oxygen at enrollment. Details of this trial based on the non-peer-reviewed data in the preliminary analysis are discussed in the Clinical Data to Date section below.[1]

Proposed Mechanism of Action and Rationale for Use in Patients with COVID-19

Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects. Both beneficial and deleterious clinical outcomes have been reported when corticosteroid (mostly prednisone or methylprednisolone) was used in other pulmonary infectious diseases. In patients with *Pneumocystis jirovecii* pneumonia and hypoxia, prednisone therapy led to decreased mortality;[2] in outbreaks of other novel coronavirus infections (i.e., Middle East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), corticosteroid therapy was associated with delayed virus clearance.[3,4] In severe pneumonia caused by influenza, corticosteroid therapy appears to worsen clinical outcomes, including secondary bacterial infection and mortality.[5]

Corticosteroids have been studied in critically ill patients with acute respiratory distress syndrome (ARDS) with conflicting results.[6-8] Seven randomized controlled trials that included 851 patients evaluated corticosteroids in ARDS.[7-13] However, when the trial results were combined by meta-analysis, corticosteroid therapy was associated with a reduction in both mortality (risk ratio 0.75; 95% confidence interval [CI], 0.59–0.95) and duration of mechanical ventilation (mean difference, -4.93 days, 95% CI, -7.81 to -2.06 days).[14,15]

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects).
- Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus, herpesviruses, strongyloidiasis, tuberculosis).
- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. As such, it may reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates.

Clinicians should review a patient's medication regimens to assess potential interactions.

- Coadministration of remdesivir and dexamethasone has not been formally studied, but a clinically significant pharmacokinetic interaction is not predicted.

Additional Considerations

- It is not known whether other corticosteroids (e.g., prednisone, methylprednisolone, or hydrocortisone) have a similar benefit as dexamethasone. The total daily dose equivalencies for dexamethasone 6 mg are prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg. Dexamethasone, a long-acting glucocorticoid with a half-life of 36 to 72 hours, is administered once daily; prednisone and methylprednisolone, both intermediate-acting agents with half-lives between 12 and 36 hours, can be administered once daily or in two divided doses daily; hydrocortisone, a short-acting glucocorticoid with a half-life of 8 to 12 hours, is generally administered in two to four divided doses daily.
- Hydrocortisone is commonly used for septic shock in patients with COVID-19; please refer to the Critical Care section for more information.
- Unlike other corticosteroids previously studied in ARDS, dexamethasone lacks mineralocorticoid activity.[10]

Considerations in Pregnancy

A short course of betamethasone and dexamethasone, which are known to cross the placenta, is routinely used to hasten fetal lung maturity and decrease the risk of neonatal respiratory distress syndrome in the premature infant with threatened delivery.[16,17]

Given the potential benefit of decreased maternal mortality, and the low risk of fetal adverse effects for this short course of therapy, the Panel recommends using **dexamethasone** in pregnant women with COVID-19 who are mechanically ventilated **(AIII)** or who require supplemental oxygen but who are not mechanically ventilated **(BIII)**.

Considerations in Children

The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Importantly, the RECOVERY trial did not include a significant number of pediatric patients, and mortality rates are significantly lower for pediatric patients with COVID-19 than for adult patients with the disease. Thus, results of this trial should be interpreted with caution for patients aged <18 years. Dexamethasone may be beneficial in pediatric patients with COVID-19 respiratory disease who are on mechanical ventilation. Use of dexamethasone in patients who require other forms of supplemental oxygen support should be considered on a case-by-case basis, and is generally not recommended for pediatric patients who require only low levels of oxygen support (i.e., nasal cannula only). Additional studies are needed to evaluate the use of steroids for the treatment of COVID-19 in pediatric patients, including in those with multisystem inflammatory syndrome in children (MIS-C).

Clinical Data to Date

Multicenter, Randomized Controlled Trial of Dexamethasone Versus Standard of Care in Hospitalized Patients

This study has not been peer reviewed.

Study Design

The RECOVERY study is a multicenter, open-label trial sponsored by the National Health Service in the United Kingdom. Eligible participants were randomized to receive one of several potential treatments for COVID-19 plus standard of care or standard of care alone. In one of the study arms, dexamethasone 6 mg daily was administered either orally or intravenously for 10 days (or until hospital discharge, whichever came first). The primary study endpoint was all-cause mortality at 28 days. Secondary endpoints included time to hospital discharge, cause-specific mortality, need for renal replacement, major cardiac arrhythmia, and receipt/duration of ventilation.[1]

Study Population

Hospitalized patients in the United Kingdom with clinically suspected COVID-19 or laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were eligible for enrollment. Patients were not enrolled into the dexamethasone study arm (or included in the analysis) if their physicians determined that the risks were too great based on their medical history or that corticosteroid therapy was definitely indicated. Recruitment was stopped by the study steering committee on June 8, 2020, when a sufficient number of participants were enrolled to assess benefit.

Preliminary Results

Participant Characteristics:

- The preliminary analysis included 6,425 participants, with 2,104 participants in the dexamethasone arm and 4,321 in the control arm.
- SARS-CoV-2 infection was confirmed by laboratory testing in 82% of the participants; confirmation of suspected infections was pending at the time of the analysis.
- The mean age of the participants was 66.1 years, 64% of participants were male, and 56% had at least one major comorbidity, including 24% with diabetes.
- At enrollment, 16% of participants required invasive mechanical ventilation, 60% had received supplemental oxygen but no invasive ventilation, and 24% required no oxygen supplementation.
- Few participants received remdesivir, hydroxychloroquine, lopinavir/ritonavir, or tocilizumab (0% to 2% of participants in either arm); approximately 7% of participants in the standard of care arm received dexamethasone after randomization. Use of azithromycin was balanced in both arms (23% vs. 24%).

Study Endpoint Analyses:

- Overall, 21.6% of participants in the dexamethasone arm and 24.6% of those in the control arm died within 28 days of study enrollment (age-adjusted rate ratio [RR] 0.83; 95% CI, 0.74–0.92, $P < 0.001$).
- There was a statistically significant interaction between baseline severity of COVID-19 and the treatment effect of dexamethasone.
  - Survival benefit was greatest among participants who required invasive mechanical ventilation at randomization: 29.0% of dexamethasone participants died within 28 days of enrollment compared with 40.7% in the control arm (RR 0.65; 95% CI, 0.51–0.82, $P < 0.001$).
  - Among patients who required supplemental oxygen but not mechanical ventilation at enrollment, 21.5% of dexamethasone participants died within 28 days of enrollment compared with 25.0% in the control arm (RR 0.80; 95% CI, 0.70–0.92, $P = 0.002$).
  - No survival benefit was seen among participants who did not require oxygen therapy at enrollment; 17.0% of dexamethasone participants died within 28 days of enrollment compared

to 13.4% in the control arm (RR 1.22; 95% CI, 0.93–1.61, $P = 0.14$).

- Secondary endpoints (e.g., cause-specific mortality, need for renal replacement, major cardiac arrhythmia) have not yet been reported.

Limitations

- The results of the RECOVERY trial have not yet been published in a peer-reviewed journal; full analysis of this study is ongoing.
- The study was randomized, but open label.
- At this time, the results of key secondary endpoints, potential adverse events, and efficacy of dexamethasone in key subgroups (e.g., age groups, patients with comorbidities) have not yet been reported.
- Study participants with COVID-19 who, according to their providers, required oxygen but not mechanical ventilation were a heterogeneous group of patients with respect to their severity of illness; it is unclear whether dexamethasone will be beneficial for other participant subsets (e.g., those who require lower versus higher levels of supplemental oxygen). There were also no standardized or objective criteria for oxygen supplementation.
- The age distribution of participants differed by respiratory status at randomization. The participants who received mechanical ventilation were more likely to be aged <70 years. Among the participants who were aged >80 years, only 1% were mechanically ventilated, while 62% and 37% were in the oxygen group and no oxygen group, respectively. Therefore, the survival benefit of dexamethasone for mechanically ventilated patients aged >80 years is unknown.
- Remdesivir was not part of the treatment in the RECOVERY trial; therefore, the safety and efficacy of coadministering remdesivir and dexamethasone are not known.
- Very few pediatric or pregnant patients with COVID-19 were included in the RECOVERY trial; therefore, the safety and efficacy of using dexamethasone in these patients are unknown.

Interpretation

In patients with severe COVID-19 who required oxygen support, the use of dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days in a preliminary analysis. The benefit of dexamethasone was most apparent in hospitalized patients who were mechanically ventilated. There was no observed benefit of dexamethasone in those not requiring oxygen support. Further clarity on the mortality benefit of dexamethasone by baseline levels of oxygenation, age, sex, comorbidities, and/or duration of symptoms would better inform application of these findings. More details regarding safety of dexamethasone and longer follow-up would assist in interpretation of this study.

Other Clinical Studies of Corticosteroids in COVID-19

Smaller retrospective cohort and case series studies have yielded conflicting results on the efficacy of corticosteroids for the treatment of COVID-19. Several of these studies demonstrated clinical benefit with the early use of low-dose methylprednisolone, including a more rapid resolution of hypoxia, reduction in requirement for mechanical ventilation, and a reduction in transfer to the intensive care unit and in-hospital length of stay. Additionally, a few of these studies[18] and a small randomized trial revealed a benefit in overall mortality in patients with moderate disease, severe disease, and ARDS,[19,20] consistent with results from the RECOVERY study.

Conversely, several publications from China, including a meta-analysis of 15 studies (which included studies for treatment of COVID-19, SARS, or MERS)[21] and a retrospective review of critically ill patients with COVID-19, suggest an increased risk of multi-organ dysfunction and no benefit in (and

potentially an increased risk of) mortality with use of corticosteroids.[22]

These studies should be interpreted with caution as they are retrospective in nature and have methodological problems.

Clinical Trials

A number of clinical trials are currently underway or in development. Please check *ClinicalTrials.gov* for the latest information.

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Interferons (Alfa, Beta)

Last Updated: July 17, 2020

Recommendation

The COVID-19 Treatment Guidelines Panel **recommends against** the use of **interferons** for the treatment of patients with severe and critical COVID-19, except in a clinical trial **(AIII)**. There are insufficient data to recommend either for or against the use of **interferon-beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.

Rationale

Studies have shown that there was no benefit when interferons were used in patients with other coronavirus infections (i.e., Middle East respiratory syndrome [MERS], severe acute respiratory syndrome [SARS]) with severe or critical disease, and the significant toxicities of interferons outweigh the potential for benefit. Interferons may have antiviral activity early in the course of the infection.

Rationale for Use in Patients with COVID-19

Interferons, a family of cytokines with antiviral properties, have been suggested as a potential treatment for COVID-19 because of their *in vitro* and *in vivo* antiviral properties.

Clinical Data for COVID-19

Combination of Interferon Beta-1b, Lopinavir/Ritonavir, and Ribavirin in the Treatment of Hospitalized Patients With COVID-19

An open-label, Phase 2 clinical trial randomized 127 participants (median age 52 years) 2:1 to combination antiviral therapy or lopinavir/ritonavir. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants hospitalized within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (interferon beta-1b 8 million units administered subcutaneously every other day for up to 7 days total, lopinavir/ritonavir, and ribavirin); those hospitalized ≥7 days after symptom onset (n = 51) were randomized to double therapy (lopinavir/ritonavir and ribavirin) because of concerns regarding potential inflammatory effects of interferon. Patients in the control group received lopinavir/ritonavir alone regardless of time from symptom onset to hospitalization. The study participants were patients in Hong Kong with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were hospitalized regardless of disease severity until they had two negative nasopharyngeal (NP) swabs.

The time to a negative result on a polymerase chain reaction SARS-CoV-2 test on an NP swab (the primary endpoint) was shorter in the combination therapy group than in the control group (median 7 days vs. 12 days, $P = 0.001$). The combination group had more rapid clinical improvement as assessed by the National Early Warning Score (NEWS) 2 and Sequential Organ Failure Assessment (SOFA) score and a shorter hospital stay (9 days vs. 14.5 days, $P = 0.016$). There was no difference in oxygen use between the groups. The antiviral and clinical effect was more pronounced in the patients hospitalized within 7 days of symptom onset suggesting that interferon beta-1b with or without ribavirin was the critical component of the combination antiviral therapy. The study provides no information about the effect of interferon beta-1b when administered ≥7 days after symptom onset.[1]

Interferon Alfa-2b Treatment for COVID-19

This study has not been peer reviewed.

In a retrospective cohort study of 77 adults with moderate COVID-19 in China, participants were treated with nebulized interferon alfa-2b, nebulized interferon alfa-2b with umifenovir (not available in the United States), or umifenovir only. The time to viral clearance in the upper respiratory tract and reduction in systemic inflammation was faster in the interferon alfa-2b groups than in the umifenovir only group. However, the results of this study are difficult to interpret because participants in the interferon alfa-2b with umifenovir group were substantially younger than those in the umifenovir only group (mean age 40 years vs. 65 years) and had fewer comorbidities (15% vs. 54%) at study entry. The nebulized interferon alfa-2b formulation is not approved by the Food and Drug Administration for use in the United States.[2]

Clinical Data for SARS and MERS

Interferon-beta used alone and in combination with ribavirin in patients with SARS and MERS has failed to show a significant positive effect on clinical outcomes.[4-8]

In a retrospective observational analysis of 350 critically ill patients with MERS[5] from 14 hospitals in Saudi Arabia, mortality was higher among patients who received ribavirin and interferon (beta-1a, alfa-2a, or alfa-2b) than among those who did not receive either drug.

A randomized clinical trial that included 301 patients with acute respiratory distress syndrome[9] found that intravenous interferon beta-1a had no benefit over placebo as measured by ventilator-free days over a 28-day period (median of 10.0 days vs. 8.5 days, respectively) or mortality (26.4% vs. 23.0%, respectively).

Clinical Trials

See *ClinicalTrials.gov* for a list of ongoing clinical trials for interferon and COVID-19.

Adverse Effects

The most frequent adverse effects of interferon-alfa include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities, elevated transaminases, and psychiatric problems (depression and suicidal ideation). Interferon-beta is better tolerated than interferon-alfa.

Drug-Drug Interactions

The most serious drug-drug interactions with interferons are the potential for added toxicity with other immunomodulators and chemotherapeutic agents.

Considerations in Pregnancy

Data from several large pregnancy registries did not demonstrate an association between exposure to interferon beta-1b preconception or during pregnancy and an increased risk of adverse birth outcomes (e.g., spontaneous abortion, congenital anomaly), and exposure did not influence birth weight, height, or head circumference.

Considerations in Children

There are limited data on the use of interferons for the treatment of respiratory viral infections in children.

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Interleukin-1 Inhibitors

Last Updated: July 17, 2020

Recommendation

- There are insufficient data to recommend for or against the use of interleukin (IL)-1 inhibitors, such as **anakinra**, for the treatment of COVID-19.

Rationale

There are case series data but no clinical trial data on the use of IL-1 inhibitors in patients with COVID-19.

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved by the Food and Drug Administration (FDA) to treat rheumatoid arthritis and cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease.[1] It is also used off-label for severe chimeric antigen receptor T cell (CAR T-cell)-mediated cytokine release syndrome (CRS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis.

Rationale for Use in Patients with COVID-19

Endogenous IL-1 is elevated in patients with COVID-19 and other conditions, such as severe CAR T-cell-mediated CRS. Case reports and case series have described favorable responses to anakinra in patients with these syndromes, including a survival benefit in patients with sepsis and reversal of cytokine storm after tocilizumab failure in adults with MAS.[2,3]

Clinical Data for COVID-19

- A case-control study compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra and 44 historical controls. The patients in both groups were all admitted to the same hospital in Paris, France. Case patients were consecutive admissions from March 24 to April 6, 2020, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or lung infiltrates on chest imaging typical of COVID-19, and either significant hypoxia (SpO_2 ≤93% with ≥6L/min O_2) or worsening hypoxia (SpO_2 ≤93% with >3L/min O_2 and a loss of ≥3% of O_2 saturation on room air in the previous 24 hours). The historic controls were patients who fulfilled the same eligibility criteria and admitted to the hospital during the same period. As standard of care for both groups, some patients received hydroxychloroquine, azithromycin, or parenteral beta-lactam antibiotics. Anakinra was dosed as 100 mg subcutaneous (SQ) twice daily for 72 hours, followed by anakinra 100 mg SQ daily for 7 days. Clinical characteristics were similar between the groups, except that the cases had a lower mean body mass index than the controls (25.5 kg/m2 vs. 29.0 kg/m^2, respectively), longer duration of symptoms (mean of 8.4 days for cases vs. 6.2 days for controls), and a higher frequency of hydroxychloroquine use (90% for cases vs. 61% for controls) and azithromycin use (49% for cases vs. 34% for controls). The primary outcome of admission to the intensive care unit for mechanical ventilation or death occurred among 13 case patients (25%) and 32 control patients (73%) (hazard ratio 0.22; 95% confidence interval, 0.11 to 0.41). However, within the first 2 days of follow up, in the control group, six patients (14%) had died and 19 patients (43%) had reached the composite primary outcome, which further limited intragroup comparisons and specifically analyses of time to event. C-reactive protein (CRP) levels decreased by Day 4 among those receiving anakinra. Thromboembolic events occurred in 10 patients (19%) who received anakinra and in five control patients (11%). The clinical implications of these findings are uncertain due to limitations in the

study design related to unmeasured confounding combined with the very high early event rate among the retrospective controls.[4]

- A single-center, retrospective cohort study compared outcomes in 29 patients following open-label use of anakinra to outcomes in 16 historical controls enrolled at the same medical center in Italy. All patients had COVID-19 with moderate to severe acute respiratory distress syndrome (ARDS) that required non-invasive ventilation and evidence of hyperinflammation (CRP ≥100 mg/L and/or ferritin ≥900 ng/mL). High-dose intravenous anakinra 5 mg/kg twice daily was administered for a median of 9 days, followed by SQ administration of anakinra 100 mg twice daily for 3 days to avoid inflammatory relapses. Patients in both the anakinra and control groups received hydroxychloroquine and lopinavir/ritonavir. In the anakinra group, reductions in CRP levels were noted over several days following anakinra initiation, and the 21-day survival rate was higher than in the control group (90% vs. 56%, respectively; $P = 0.009$). However, the patients in the anakinra group were younger than those in the control group (median age 62 years vs. 70 years, respectively), and fewer patients in the anakinra group had chronic kidney disease. High-dose anakinra was discontinued in seven patients (24%) because of adverse events (four patients developed bacteremia and three patients had elevated liver enzymes); however, retrospective assessment showed that these events occurred with similar frequency in the control group. An additional group of seven patients received low-dose SQ anakinra 100 mg twice daily; however, treatment in this group was stopped after 7 days because of lack of clinical or anti-inflammatory effects.[5]
- Other small case series have reported anakinra use for the treatment of COVID-19 and anecdotal evidence of improvement in outcomes.[6]

Clinical Trials

See *ClinicalTrials.gov* for a list of clinical trials evaluating anakinra for the treatment of COVID-19.

Adverse Effects

Anakinra was not associated with any significant safety concerns when used in clinical trials for the treatment of sepsis.[7-9] Increased rates of infection were reported with prolonged anakinra use in combination with tumor necrosis factor-alpha blockade, but not with short-term use.[10]

Considerations in Pregnancy

There is limited evidence on which to base a recommendation in pregnancy, but unintentional first trimester exposure is unlikely to be harmful.[11]

Considerations in Children

Anakinra has been used extensively in the treatment of severely ill children with complications of rheumatologic conditions, including MAS. Pediatric data on the use of anakinra in ARDS/sepsis are limited.

Drug Availability

Procuring anakinra may be a challenge at some hospitals in the United States. Anakinra is FDA-approved only for SQ injection.

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Interleukin-6 Inhibitors

Last Updated: June 11, 2020

Recommendation

- There are insufficient data to recommend either for or against the use of **interleukin-6 (IL-6) inhibitors** (e.g., **sarilumab**, **siltuximab**, **tocilizumab**) for the treatment of COVID-19.

Rationale

There are insufficient data from clinical trials on the use of IL-6 inhibitors in patients with COVID-19.

Rationale for Use in Patients with COVID-19

IL-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the related SARS-associated coronavirus induces a dose-dependent production of IL-6 from bronchial epithelial cells.[1] Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. COVID-19-associated systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin.[2-4]

Sarilumab

Sarilumab is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that is approved by the Food and Drug Administration (FDA) for use in patients with rheumatoid arthritis. It is available as a subcutaneous (SQ) formulation and is not approved for cytokine release syndrome (CRS). A placebo-controlled clinical trial is evaluating the use of an intravenous (IV) formulation administered as a single dose for COVID-19.

Clinical Data for COVID-19

Press Release, April 27, 2020: In a Phase 2/3 clinical trial (*ClinicalTrials.gov* identifier NCT04315298), hospitalized COVID-19 patients were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Preliminary data were released after an Independent Data Monitoring Committee recommended discontinuing the 200-mg arm and restricting future enrollment to critical patients only. At the time of the interim review of the first 457 participants enrolled, 145 were randomized to receive sarilumab 400 mg, 136 to receive sarilumab 200 mg, and 77 to receive placebo. At study entry, 28% of the patients had severe illness, 49% had critical illness, and 23% had multisystem organ dysfunction.[5]

Sarilumab decreased CRP, which changed by -79%, -77%, and -21% in the sarilumab 400 mg group, sarilumab 200 mg group, and placebo group, respectively (this is the primary outcome measure of the Phase 2 trial).

At the time of data analysis, the percentage of patients with critical illness (n = 226) who died or were on a ventilator was lower in the sarilumab 400 mg group (28%) than in the sarilumab 200 mg group (46%) and in the placebo group (55%). Comparing mortality alone, the percentage of patients who died also was lower in the sarilumab 400 mg group (23%) than in the sarilumab 200 mg group (36%) and in the placebo group (27%). In contrast to the positive trend in outcomes among patients with critical illness who received sarilumab, the April 27, 2020, press release about the study cited "negative trends" for most outcomes in patients with severe illness who received the drug.

Adverse Effects

The primary lab abnormalities that have been reported with sarilumab treatment are transient and/or reversible elevations in liver enzymes that appear to be dose dependent and rare occurrences of neutropenia and thrombocytopenia. Risk for serious infections (e.g., tuberculosis [TB], other bacterial pathogens) have been reported only in the context of long-term use of sarilumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Drug Availability

The SQ formulation of sarilumab is not approved for CRS. The IV formulation is not approved by the FDA, but it is being studied in a clinical trial of hospitalized patients with COVID-19. A list of current clinical trials is available at *ClinicalTrials.gov*.

Siltuximab

Siltuximab is a recombinant human-mouse chimeric monoclonal antibody that binds IL-6 and that is approved by the FDA for use in patients with Castleman's disease. Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6R, inhibiting IL-6 signaling. Siltuximab is dosed as an IV infusion.

Clinical Data in COVID-19

There are limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19.[6] There are no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections (i.e., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome.

Clinical Trials

See *ClinicalTrials.gov* for a list of current clinical trials for siltuximab and COVID-19.

Adverse Effects

The primary adverse effects (AEs) reported for siltuximab have been related to rash. Additional AEs, such as serious bacterial infections, have been reported only in the context of long-term dosing of siltuximab once every 3 weeks.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Drug Availability

Procuring siltuximab may be a challenge at some hospitals in the United States.

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody that is approved by the FDA for use in patients with rheumatologic disorders and CRS induced by chimeric antigen receptor T cell (CAR-T) therapy. Tocilizumab can be dosed for IV or SQ injection. For CRS, the IV formulation should be used.[7]

Clinical Data for COVID-19

- *Press Release, April 27, 2020:* The CORIMUNO-TOCI trial (*ClinicalTrials.gov* identifier NCT04331808) is an open-label, randomized trial of hospitalized patients with COVID-19 (n = 129 at seven sites in France) who had moderate or severe disease at study entry and who were randomized to receive tocilizumab plus standard of care (n = 65) or standard of care alone (n = 64). Patients received tocilizumab 8 mg/kg on Day 1. If there was no response to the treatment (i.e., no decrease in oxygen requirement), a second infusion of tocilizumab was administered on Day 3. In this preliminary report, the proportion of participants who had died or who needed ventilation (noninvasive or mechanical) was lower in the tocilizumab group than in the standard of care group. Detailed results of the trial have not been reported. The Data and Safety Monitoring Board resigned after the press release was issued.[8]
- *Published study:* Sixty-three hospitalized adult patients with COVID-19 were enrolled in a prospective, open-label study of tocilizumab for severe COVID-19. Criteria for inclusion in the study were polymerase chain reaction-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; pulmonary involvement, assessed either by oxygen saturation ($Sa0_2$) <93% on room air or PaO_2/FiO_2 ratio <300 mm Hg; and at least three of the following: CRP >10 times normal values, ferritin >1,000 ng/mL, D-dimer >10 times normal values, or lactate dehydrogenase >2 times the upper level of normal. The patients' mean age was 62.6 years and most (88%) were male; 39.7% of the patients were febrile, and 95.7% had bilateral pulmonary infiltrates. Five patients were on mechanical ventilation at baseline. All of the patients received off-label antiretroviral protease inhibitors. Patients received either tocilizumab IV (8 mg/kg) or tocilizumab SQ (324 mg); within 24 hours after this initial dose, a second dose was administered to 52 of the 63 patients. Following administration of tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The mean PaO_2/FiO_2 ratio of the patients increased between admission (152 +/- 53 mm Hg) and Day 7 of hospitalization (284 +/- 116 mm Hg). No moderate or severe adverse events attributable to tocilizumab were reported. The overall mortality rate was 11% (7 of 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association between earlier use of tocilizumab and reduced mortality; however, interpretation of this result is limited because the study results did not describe a comparison group or specify an a priori comparison.[9]

Clinical Trials

See *ClinicalTrials.gov* for ongoing trials that are evaluating the use of tocilizumab for the treatment of COVID-19.

Adverse Effects

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional AEs, such as risk for serious infections (e.g., TB, other bacterial pathogens), have been reported only in the context of continuous dosing of tocilizumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Considerations in Children

In children, tocilizumab is frequently used for CRS following CAR-T therapy[10] and it is occasionally used for MAS.[11] Pediatric data for its use in ARDS/sepsis are limited.

Drug Availability

Procuring IV tocilizumab may be a challenge at some hospitals in the United States.

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Kinase Inhibitors: Bruton's Tyrosine Kinase Inhibitors and Janus Kinase Inhibitors

Last Updated: July 17, 2020

Recommendation

The COVID-19 Treatment Guidelines Panel **recommends against** the use of **Bruton's tyrosine kinase (BTK) inhibitors**, such as **acalabrutinib**, **ibrutinib**, and **zanubrutinib**; and **Janus kinase (JAK) inhibitors**, such as **baricitinib**, **ruxolitinib**, and **tofacitinib**; for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Rationale

BTK inhibitors and JAK inhibitors have broad immunosuppressive effects. Ongoing clinical trials should help clarify their role in the treatment of COVID-19.

BTK inhibitors are licensed by the Food and Drug Administration (FDA) for the treatment of B-cell malignancies.[1] BTK is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion.[2]

JAK inhibitors are potent immunosuppressive agents that are FDA approved for the treatment of rheumatoid arthritis, psoriatic arthritis, polycythemia vera, myelofibrosis, ulcerative colitis, and graft-versus-host disease. JAK inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins[3,4] that are involved in vital cellular functions, including signaling, growth, and survival. Phosphorylation of STAT proteins involved in these pathways can increase or decrease their function, and aberrant activation of these proteins has been associated with autoimmune disorders and cancers.[5] JAKs transmit cytokine signaling by pairing with another JAK (e.g., JAK1/JAK2, JAK1/JAK3); however, whether inhibition of specific JAKs is relevant to therapeutic effectiveness is unknown.

Rationale for Use in Patients With COVID-19

The kinase inhibitors are proposed as treatments for COVID-19 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6).[6] This immunosuppression could potentially reduce the inflammation and associated immunopathologies that have been observed in patients with COVID-19. Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry into and infection of susceptible cells.[7]

Adverse Effects

Most of the data on adverse effects of BTK and JAK inhibitors refer to chronic use of the agents. Adverse effects include infections (typically respiratory and urinary tract infections) and the reactivation of herpes viruses. Additional toxicities include myelosuppression and transaminase elevations. Hemorrhage and cardiac arrhythmia have occurred in patients who received BTK inhibitors. Thrombotic events and gastrointestinal perforation have occurred in patients who received JAK inhibitors.

Considerations in Pregnancy

- BTK inhibitors: There is a paucity of data on human pregnancy and BTK inhibitor use. In

animal studies, in doses exceeding the therapeutic human dose, acalabrutinib and ibrutinib were associated with interference with embryofetal development.[8,9] Based on these data, BTK inhibitors may be associated with fetal malformations when use occurs during organogenesis. The impact of use later in pregnancy is unknown. Risks of use should be balanced against potential benefits.

- JAK inhibitors: There is a paucity of data on the use of JAK inhibitors in pregnancy. Fetal risk cannot be ruled out. Pregnancy registries provide some outcome data on tofacitinib used during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis). Among the 33 cases reported, pregnancy outcomes were similar to those among the general pregnant population.[10-12] Risks of use should be balanced against potential benefits.

Bruton's Tyrosine Kinase Inhibitors

Acalabrutinib

Acalabrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat B-cell malignancies (i.e., chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma). It has a better toxicity profile than first-generation BTK inhibitors (e.g., ibrutinib) due to less off-target activity for other kinases.[13] Acalabrutinib is proposed for use in patients with COVID-19 because it can modulate signaling that promotes inflammation.

Clinical Data for COVID-19

Data regarding acalabrutinib are limited to a retrospective case series of 19 patients with severe COVID-19.[14] However, data interpretation to discern any clinical benefit is limited by the study's small sample size and lack of a control group.

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information on studies of acalabrutinib and COVID-19.

Ibrutinib

Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies[9] and prevent chronic graft-versus-host disease in stem cell transplant recipients.[15] Based on results from a small case series, ibrutinib has been theorized to improve inflammation and protect against ensuing lung injury in patients with COVID-19.[16]

Clinical Data for COVID-19

Data regarding ibrutinib are limited to an uncontrolled, retrospective case series of six patients with COVID-19 who were receiving ibrutinib for a condition other than COVID-19.[16] However, evaluation of the data for any clinical benefit is limited by the series's small sample size and lack of a control group.

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information on studies of ibrutinib and COVID-19.

Zanubrutinib

Zanubrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat mantle cell lymphoma.[17] It has been shown to have fewer toxicities than first-generation BTK inhibitors (e.g., ibrutinib) due to less off-target activity for other kinases.[18] Zanubrutinib is proposed to be of use in patients with COVID-19 by modulating signaling that promotes inflammation.

Clinical Data for COVID-19

There is no clinical data on the use of zanubrutinib to treat COVID-19.

Clinical Trials

Please check ClinicalTrials.gov for the latest information on studies of zanubrutinib and COVID-19.

Janus Kinase Inhibitors

Baricitinib

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2 and FDA approved for the treatment of rheumatoid arthritis.[19] Among the JAK inhibitors studied, baricitinib has been postulated to have the greatest theoretical antiviral efficacy in inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from entering and infecting lung cells because of its affinity for adaptor-associated kinase-1 (AAK1), a regulator of viral endocytosis in pulmonary alveolar type 2 (AT2) epithelial cells.[20] In addition, baricitinib can modulate downstream inflammatory responses via inhibition of JAK1/JAK2 kinase and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.[21]

Clinical Data for COVID-19

This study has not been peer-reviewed.

A small, nonrandomized study in patients with moderate COVID-19 pneumonia compared combination therapy with baricitinib and lopinavir/ritonavir to standard of care (SOC) therapy (i.e., combination lopinavir/ritonavir and hydroxychloroquine). Both study groups included 12 patients. Compared to SOC therapy, combination therapy with baricitinib and lopinavir/ritonavir demonstrated a statistically significant shorter time to improvement of clinical and respiratory symptoms and a greater reduction of C-reactive protein levels.[22]

Clinical Trials

Please check ClinicalTrials.gov for the latest information on studies of baricitinib and COVID-19.

Ruxolitinib

Ruxolitinib is an oral JAK inhibitor selective for JAK1 and JAK2 and is currently approved for myelofibrosis, polycythemia vera, and acute graft-versus-host disease.[23] Like baricitinib, it is theorized to have antiviral properties through inhibition of AAK1, which may prevent viral entry and infection of pulmonary AT2 epithelial cells.[7]

Clinical Data for COVID-19

A small, prospective, single-blind, randomized controlled Phase 2 trial in patients with COVID-19 in China compared ruxolitinib 5 mg orally twice daily (n = 20) with placebo (administered as vitamin C 100 mg; n = 21), both given in combination with SOC therapy. The median age of the patients was 63 years. There were no significant demographic differences between the two arms. Treatment with ruxolitinib was associated with a nonsignificant reduction in the median time to clinical improvement (12 days for ruxolitinib vs. 15 days for placebo; $P = 0.15$), defined as a two-point improvement on a seven-category ordinal scale or as hospital discharge. There was no difference between the groups in the median time to discharge (17 days for ruxolitinib vs. 16 days for placebo; $P = 0.94$). More patients in the ruxolitinib group than in the placebo group had radiographic improvement on computerized tomography scans of the chest at Day 14 (90% for ruxolitinib vs. 61.9% for placebo; $P = 0.05$) and a shorter time to recovery from initial lymphopenia (5 days for ruxolitinib vs. 8 days for placebo; $P = 0.03$), when it was present. The use of ruxolitinib was not associated with an increased risk of adverse events or mortality (no deaths in the ruxolitinib group vs. three deaths [14%] in the control group). Despite the theoretical antiviral properties of JAK inhibitors, there was no significant difference in the time to viral clearance

among the patients who had detectable viral loads at the time of randomization to ruxolitinib treatment (n = 8) or placebo (n = 9). Limitations of this study include the small sample size, the exclusion of ventilated patients at study entry, and the frequent concomitant use (among 70% of patients) of antivirals and steroids.[24]

A small, retrospective, single-arm study in Germany reported no safety concerns in 14 patients with severe COVID-19 who received a brief course of ruxolitinib therapy (with a median of 9 days of treatment).[25]

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information on studies of ruxolitinib and COVID-19.

Tofacitinib

Tofacitinib is the prototypical JAK inhibitor, predominantly selective for JAK1 and JAK3, with modest activity against JAK2, and, as such, can block signaling from gamma-chain cytokines (e.g., IL-2, IL-4) and gp 130 proteins (e.g., IL-6, IL-11, interferons). It is an oral agent first approved for the treatment of rheumatoid arthritis and has been shown to decrease levels of IL-6 in patients with this disease.[26] Tofacitinib is also FDA approved for the treatment of psoriatic arthritis and ulcerative colitis.[27]

Clinical Data for COVID-19

There is no clinical data on the use of tofacitinib to treat COVID-19.

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information on studies of tofacitinib and COVID-19.

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Table 3a. Immune-Based Therapy Under Evaluation for Treatment of COVID-19: Clinical Data to Date

Last Updated: July 17, 2020

Information presented in this table may include data from pre-print/non-peer reviewed articles. This table will be updated as new information becomes available.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products			
COVID-19 Convalescent Plasma	• The FDA has provided recommendations for the use of COVID-19 convalescent plasma through EINDs for individual patients, traditional INDs, or expanded access INDs. The FDA has also approved a national expanded access program for the use of convalescent plasma for the treatment of patients with COVID-19. Clinicians can refer to the National COVID-19 Convalescent Plasma Project website for more information on that specific program and other trials evaluating convalescent plasma.	• Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2.[1] Thousands of U.S. patients have received convalescent plasma through clinical trials, expanded access treatment trials, and EIND applications. However, the standards and methods for screening donated plasma for SARS-CoV-2 binding and neutralizing antibodies have not been established. The variability in SARS-CoV-2 antibody levels in donor plasma may impact the product's efficacy. Clinical data are currently insufficient to evaluate the efficacy of convalescent plasma.	**For COVID-19:** • *Open-Label, Randomized Clinical Trial of Convalescent Plasma in 103 Hospitalized Patients With Severe or Life-Threatening COVID-19:* Investigators conducted an open-label, randomized clinical trial of convalescent plasma versus SOC for patients with severe and life-threatening laboratory-confirmed COVID-19 in seven medical centers in Wuhan, China, from February 14 to April 1, 2020. The primary outcome was time to clinical improvement within 28 days, which was defined as patient discharged alive or a reduction of 2 points on a 6-point disease severity scale. Only plasma units with SARS-CoV-2 viral spike-receptor binding domain-specific IgG titer ≥ 1:640 were transfused. The median dose of ABO-compatible convalescent plasma was 200 mL. The time from symptom onset to randomization was 27 days in the treatment group and 30 days in the control group. Due to control of the COVID-19 outbreak in Wuhan, the trial was terminated early after 103 of the planned for 200 patients were enrolled. The convalescent plasma and control groups were well balanced by age (median age of 70 years vs. 69 years, respectively), but the control group had a higher proportion of men (65%) than the convalescent plasma group (52%). Baseline severity scores (45 patients had severe disease and 58 had life-threatening disease) and use of concomitant therapies were similar between the two groups. There was no significant difference between the groups in the primary outcome of time to clinical improvement within 28 days (HR 1.40; 95% CI, 0.79–2.49; $P = 0.26$). Among those with severe disease, 91% of the convalescent plasma recipients and 68% of the control patients improved by Day 28 (difference 23%; OR 1.34; 95% CI, 0.98–1.83; $P = 0.07$). Among those with life-threatening disease, 21% of the convalescent plasma recipients and 24% of the control patients improved by Day 28 (difference -3.4%; OR 0.86; 95% CI, 0.33–2.24; $P = 0.75$). There was no significant difference in 28-day mortality between the groups (16% vs. 24% for the treatment and control groups, respectively; OR 0.65; 95% CI, 0.29–1.46; $P = 0.30$). At 24, 48, and 72 hours, the rates of negative SARS-CoV-2 viral PCR were significantly higher in the convalescent plasma group than in the control group (45% vs. 15%, $P = 0.003$ at 24 hours; 68% vs. 33%, $P = 0.001$ at 48 hours; and 87% vs.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products, continued			
COVID-19 Convalescent Plasma, continued			38%, *P* <0.001 at 72 hours). Two transfusion-related events were reported, including 1 severe event; both events resolved with supportive care. The study's primary limitations were its open-label design and that, on average, administration of the convalescent plasma was approximately 1 month into the disease course. In addition, the study was terminated early, and thus the sample size was insufficient to detect differences in clinical outcomes.[2] • *Preliminary Safety Analysis of the First Consecutive 5,000 Patients to Receive Open Label, COVID-19 Convalescent Plasma Through a National Expanded Access Program:*[3] The Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19 program is an ongoing, open-label, nonrandomized protocol primarily designed to provide patients with severe or life-threatening (critical) COVID-19 with access to convalescent plasma, which is an investigational product in the United States. Secondary objectives were to obtain safety data on the product. The protocol is sponsored by the Mayo Clinic and includes a diverse range of clinical sites. Plasma donors have documented COVID-19, with complete resolution of symptoms for at least 14 days prior to donation, and are either male, female without history of pregnancy, or female with history of pregnancy and negative HLA testing after the most recent pregnancy. SARS-Cov-2 antibody testing of donors is not mandated. ABO-compatible convalescent plasma is transfused preferentially, but in the absence of ABO-compatible plasma, patients may receive either Group A plasma or low anti-A titer Group O plasma, as available. The main safety outcomes for the safety analysis are SAEs including death; SAEs are reported at 4 hours and at 7 days after transfusion, or as they occur. The safety analysis describes the first 5,000 patients, enrolled between April 7 and May 3, 2020. Participants were adults with median age of 62 years, 63% male, and 81% had severe or life-threatening COVID-19. SAEs were reported in 36 patients (<1%) within 4 hours of transfusion; SAEs included 15 deaths, including 4 possibly or probably related to the convalescent plasma treatment. The 21 non-fatal SAEs included 7 TACO events, 11 TRALI events, and 3 severe allergic reactions. The overall 7-day mortality rate was 14.9%. In this study, COVID-19 convalescent plasma therapy was associated with a low rate (<1%) of serious transfusion-related events. The study design, which does not include a control arm, precludes an assessment of efficacy or ADE. • *Retrospective, Single-Center, Case-Control Study Evaluating Convalescent Plasma Plus Standard of Care Versus Standard of Care Without Convalescent Plasma:*[4] *Not Peer Reviewed.* This case-control study reports clinical outcomes among 39 consecutive patients who received COVID-19 convalescent plasma through the FDA's single patient EIND program while hospitalized at Mount Sinai Hospital in New York City during the

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products, continued			
COVID-19 Convalescent Plasma, continued			period March 24 to April 8, 2020. Recipients were transfused with 2 units of ABO-compatible convalescent plasma from donors with a SARS-CoV-2 antispike antibody titer of 1:320 dilution. The control group (n = 156) was identified retrospectively from the hospital's EHR database. The control patients were hospitalized during the same period as the patients in the convalescent plasma group and had confirmed COVID-19 but did not receive convalescent plasma. They were matched 4:1 to the convalescent plasma recipients using propensity scores to correct for measured confounders. Convalescent plasma recipients had a mean age of 55 years and 64% were male. At the time of transfusion, 87% of the recipients required supplemental oxygen (noninvasive) and 10% were mechanically ventilated. By Day 14, the clinical condition had worsened in 18% of the convalescent plasma patients and 24% of the control patients ($P = 0.17$). As of May 1, 2020, 13% of the plasma recipients and 24% of the matched control patients had died ($P = 0.04$, log-rank test) and 72% of the transfused patients and 67% of the control patients had been discharged. Interpretation of the study results is limited by the lack of randomization and the potential for unmeasured patient selection bias. • Other smaller, uncontrolled case series describing clinical outcomes in patients with COVID-19 have been reported and also suggest that serious AEs are uncommon following COVID-10 convalescent plasma treatment.[5-10]
SARS-CoV-2 Specific Immunoglobulins	• Not approved by the FDA	• Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response.	• No clinical data for COVID-19, SARS, or MERS

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products, continued			
Non-SARS-CoV-2 Specific Intravenous Immunoglobulins	• Primary immune disorders • Thrombocytopenic purpura • Kawasaki disease • Motor neuropathy • Prophylaxis of various bacterial and viral infections	• Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, products derived from the plasma of donors without confirmation of SARS-CoV-2 infection are not likely to contain SARS-CoV-2 antibodies. Furthermore, although IVIG contains other blood components that may have general immunomodulatory effects, it is unclear if these theoretical immunomodulatory effects will benefit patients with COVID-19.	**For COVID-19:** • *Not Peer Reviewed.* A retrospective, nonrandomized cohort study of IVIG for the treatment of COVID-19 was conducted across eight treatment centers in China between December 2019 and March 2020. The study found no difference in 28-day or 60-day mortality between 174 patients who were treated with IVIG and 151 patients who were not treated with IVIG. Patients who received IVIG were hospitalized for longer (median stay of 24 days for IVIG group vs. 16 days for no IVIG group) and experienced longer duration of disease (median of 31 days for IVIG group vs. 23 days for no IVIG group). It should be noted that a higher proportion of IVIG-treated patients had severe disease at study entry (71 patients [41%] with critical status in the IVIG group vs. 32 patients [21%] in the non-IVIG group). A subgroup analysis that was limited to the critically patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days. The results are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive IVIG or no IVIG, and the patients in the IVIG group were older and more likely to have coronary heart disease than those in the no IVIG group. The IVIG group also had more patients with severe COVID-19 disease at study entry. Also, patients in both groups received many concomitant therapies for COVID-19.[11]
Mesenchymal Stem Cells (MSCs)	• Not approved by the FDA	• Multipotent adult stem cells that are present in most human tissues including the umbilical cord • It is hypothesized that MSCs could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by SARS-COV-2. • MSCs lack the angiotensin-converting enzyme 2 receptor that SARS COV-2 uses for viral entry into cells; therefore, MSCs are resistant to infection.[12,13]	**For COVID-19:** • A pilot study of IV MSC transplantation in China enrolled 10 patients with confirmed COVID-19 categorized according to the National Health Commission of China criteria as critical, severe, or common-type disease. Seven patients (1 with critical illness, 4 with severe illness, and 2 with common-type illness) received MSCs; 3 patients with severe illness received placebo. All 7 patients who received MSCs recovered. Among the 3 severely ill control patients, 1 died, 1 developed ARDS, and 1 remained stable with severe disease.[14] **For Other Viruses:** • In an open-label study of MSCs for the treatment of H7N9 influenza in China, 17 patients received MSC treatment plus SOC, and 44 patients received SOC only. In the MSC group, 3 patients (17.6%) died; in the control group, 24 patients (54.5%) died. The 5-year follow-up was limited to 5 patients in the MSC group. No safety concerns were identified.[15]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Immunomodulators			
Corticosteroids			
Dexamethasone	**FDA-Approved Indications:** • Allergic states (e.g., severe or incapacitating asthma, dermatitis, drug HSRs) • Dermatologic diseases (e.g., bullous dermatitis, Stevens-Johnson syndrome) • Endocrine disorders (e.g., adrenocortical insufficiency) • Gastrointestinal diseases (e.g., ulcerative colitis) • Hematologic disorders (e.g., hemolytic anemia, idiopathic thrombocytopenia purpura, pure red cell aplasia) • Neoplastic diseases (e.g., palliative treatment of leukemia, lymphoma) • Nervous system disorders (e.g., multiple sclerosis, cerebral edema) • Ophthalmic diseases (e.g., temporal arteritis, uveitis) • Renal diseases (e.g., to induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome) • Respiratory diseases (e.g., eosinophilic pneumonia) • Rheumatic disorders (e.g., ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus)[16]	• Long-acting potent synthetic glucocorticoid with minimal mineralocorticoid activity. Glucocorticoid activity includes anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects.[17] • Potent anti-inflammatory effects may mitigate or prevent the systemic inflammatory response associated with severe COVID-19.	**For COVID-19:** • A preliminary, unpublished analysis from a large multicenter, randomized, open-label trial (RECOVERY) in hospitalized patients in the United Kingdom showed that those randomized to dexamethasone 6 mg daily (n = 2,104) had reduced mortality within 28 days of enrollment compared with those who received SOC (n = 4,321) (21.6% vs. 24.6%; RR 0.83; 95% CI, 0.74–0.92, $P < 0.001$). The survival benefit was greatest among participants who required invasive mechanical ventilation at randomization: 29.0% of participants in the dexamethasone group died within 28 days of enrollment compared with 40.7% of those in the control arm (RR 0.65; 95% CI, 0.51–0.82, $P < 0.001$). Among patients who required supplemental oxygen but not mechanical ventilation at enrollment, 21.5% in the dexamethasone arm died within 28 days of enrollment compared with 25.0% of those in the control arm (RR 0.80; 95% CI, 0.70–0.92, $P = 0.002$). No survival benefit was seen among participants who did not require oxygen therapy at enrollment; 17.0% of dexamethasone participants died within 28 days of enrollment compared with 13.4% in the control arm (RR 1.22; 95% CI, 0.93–1.61, $P = 0.14$). Interpretation of these results is limited by several factors: full analysis of the trial is ongoing; the results of key secondary endpoints, potential adverse events, and efficacy in key subgroups have not been reported; there were not standardized or objective criteria for oxygen supplementation; and the age distribution of patients differed by respiratory status at the time of randomization (patients who received mechanical ventilation were more likely to be <70 years of age).[18] • Small retrospective cohort studies and case series have yielded conflicting results regarding corticosteroids, with some suggesting benefits associated with short courses of corticosteroids[19-22] and others showing potential harm.[23,24] • Conversely, several publications from China including a meta-analysis of 15 studies (which included studies for treatment of COVID-19, SARS, or MERS)[24] and a retrospective review of critically ill patients with COVID-19 suggest an increased risk of multi-organ dysfunction and no benefit in (to possibly increased risk of) mortality with use of corticosteroids.[25]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Interferon Alfa and Interferon Beta			
Interferon Alfa	• IFN alfa-2b: Leukemia, melanoma, lymphoma, condylomata acuminata, Kaposi sarcoma, hepatitis B, hepatitis C • IFN alfa-1b is not available in the United States.	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types[26-28]	**For COVID-19:** • An open-label, Phase 2 clinical trial randomized 127 participants (median age 52 years) 2:1 to combination antiviral therapy or LPV/r. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants admitted within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (IFN beta-1b 8 million units SQ every other day for up to 7 days total, LPV/r, and ribavirin); those admitted ≥7 days after symptom onset (n = 51) were randomized to double therapy (LPV/r and ribavirin) because of concerns regarding potential inflammatory effects of IFN. All participants in the control group received LPV/r alone regardless of time from symptom onset to hospitalization. The study participants were patients in Hong Kong with confirmed SARS-CoV-2 infection who were hospitalized regardless of disease severity until they had two negative nasopharyngeal swabs. The median time to a negative SARS-CoV-2 PCR on a nasopharyngeal swab (the primary endpoint) was shorter for the combination group than for the control group (7 days vs. 12 days, $P = 0.001$). The combination group had more rapid clinical improvement as assessed by NEWS2 and SOFA score and a shorter hospital stay (9 days for combination group vs. 14.5 days for control group, $P = 0.016$). There was no difference in oxygen use between the groups. The antiviral and clinical effect was more pronounced in the patients hospitalized within 7 days of symptom onset suggesting that IFN beta-1b with or without ribavirin was the critical component of the combination therapy. The study provides no information about the effect of IFN beta-1b administered >7 days after symptom onset.[29] • *Not Peer Reviewed.* In a retrospective cohort study of 77 adults with moderate COVID-19 in China, those who used nebulized IFN alfa-2b with or without umifenovir (Arbidol) achieved viral clearance in the upper respiratory track faster and had lower systemic inflammation than those who used only umifenovir. However, results are difficult to interpret because participants in the IFN alfa-2b group were substantially younger than those in the umifenovir only group (mean age 40 years vs. 65 years) and had fewer comorbidities (15% vs. 54%) at study entry. The nebulized formulation of IFN alfa-2b is not FDA approved for use in the United States.[30]
Interferon Beta	• Multiple sclerosis (IFN beta-1a, IFN beta-1b)	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types (T cell, B cell, and cytokine function)[26,31] • Among IFN subtypes, IFN beta-1b shows greatest *in vitro* inhibition of MERS-CoV.[32,33] • *In vitro* activity against MERS-CoV in lung cells.[34]	

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Interleukin-1 Inhibitor			
Anakinra	• Rheumatoid arthritis • Cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease[35] • IV formulation is not approved for use in the United States	• Competitively inhibits IL-1 binding to the IL-1 type I receptor	**For COVID-19:** • A case-control study compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra to outcomes in 44 historical controls. The patients in both groups were admitted to the same hospital system in Paris, France. Cases were consecutive admissions from March 24 to April 6, 2020, with laboratory-confirmed SARS-CoV-2 infection or lung infiltrates on chest imaging typical of COVID-19, and either significant hypoxia (SpO_2 ≤93% with ≥6L/min O_2) or worsening hypoxia (SpO_2 ≤93% with >3L/min O_2 and a loss of ≥3% of O_2 saturation on room air in the previous 24 hours). Historic controls were patients fulfilling the same eligibility criteria and admitted to the hospital from March 18 to March 24, 2020. SOC for both groups entailed use of HCQ, AZM, and parenteral beta-lactam antibiotics. Anakinra was dosed SQ as 100 mg twice daily for 72 hours, followed by anakinra 100 mg daily for 7 days. Clinical characteristics were similar between the groups, except that the case patients had a lower mean BMI (25.5 kg/m^2 for cases vs. 29.0 kg/m^2 for controls), longer duration of symptoms (8.4 days for cases vs. 6.2 days for controls), and a higher frequency of HCQ use (90% for cases vs. 61% for controls) and AZM use (49% for cases vs. 34% for controls). The primary outcome of either admission to the ICU for mechanical ventilation or death occurred among 13 cases (25%) and 32 controls (73%) (HR 0.22; 95% CI, 0.11–0.41). However, within the first 2 days of follow up, in the control group, 6 patients (14%) had died and 19 patients (43%) had reached the composite primary outcome, which further limited intragroup comparisons and specifically analyses of time to event. CRP levels decreased by Day 4 among those receiving anakinra. Thromboembolic events occurred in 10 patients (19%) in the anakinra group and 5 patients (11%) in the control group. The clinical implications of these findings are uncertain, due to limitations in the study design related to unmeasured confounding combined with the very high early event rate among the retrospective controls.[36] • A single-center case series reported on open-label use of anakinra in 9 hospitalized patients with COVID-19, presenting with 4–12 days of symptoms, requiring oxygen ≤6 L/min, and serum CRP ≥50 mg/L. Anakinra was administered SQ, 100 mg every 12 hours for 3 days followed by 100 mg daily for up to 7 more days. Two patients also received HCQ plus AZM; the other 7 patients received no specific additional treatments. Anakinra was discontinued in one patient who progressed to acute respiratory failure after the first dose of

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Interleukin-1 Inhibitor, continued			
Anakinra			the drug. Good clinical outcomes were observed in the other eight patients as assessed by oxygen flow, decline in CRP, and no progression in infiltrates on serial CT scans. Three patients had elevated liver transaminase levels. Results are difficult to interpret because of the low number of patients in the case series, the short follow-up, and the absence of a comparison group.[37] • A single-center, retrospective, cohort study in Italy compared outcomes in 29 patients following open-label anakinra use with outcomes in 16 historical controls. All patients had COVID-19 with moderate to severe ARDS requiring noninvasive ventilation, and evidence of hyperinflammation. High-dose IV anakinra 5 mg/kg twice daily was administered for a median of 9 days, followed by SQ administration (anakinra 100 mg twice daily) for 3 days to avoid inflammatory relapses. Both the anakinra and control (standard treatment) groups received HCQ and LPV/r. In the high-dose anakinra group, reductions in CRP levels were noted following anakinra initiation. The 21-day survival rate was 90% in the anakinra group and 56% in the control group (P = 0.009); however, the patients in the anakinra group were younger (median age of 62 years in anakinra group vs. 70 years in control group), and fewer patients had chronic kidney disease. High-dose anakinra was discontinued in 7 patients (24%) due to AEs (bacteremia in 4 patients, elevated liver enzymes in 3 patients); however, retrospective assessment showed that these events occurred with similar frequency in the control group. An additional group of 7 patients received low-dose SQ anakinra (100 mg twice daily); however, treatment in this group was stopped after 7 days because of lack of clinical or anti-inflammatory effects.[38]
Interleukin-6 Inhibitors Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in some patients with COVID-19; IL-6 inhibition may reduce these effects.			
Sarilumab	• Rheumatoid arthritis[39]	• Human recombinant monoclonal antibody • IL-6 receptor antagonist[40]	**For COVID-19:** • *Press Release:* In a Phase 2/3 clinical trial (*ClinicalTrials.gov* Identifier NCT04315298), hospitalized COVID-19 patients were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Preliminary data were released after an IDMC recommended discontinuing the 200-mg arm and restricting future enrollment to critically patients only. Of the first 457 participants enrolled, 145 were randomized to sarilumab 400 mg, 136 to sarilumab 200 mg, and 77 to placebo. At study entry, 28% of the patients had severe illness, 49% had critical illness, and 23% had multisystem organ

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Interleukin-6 Inhibitors, continued			
Sarilumab			dysfunction. Sarilumab decreased CRP, which changed by -79%, -77%, and -21% in the sarilumab 400 mg group, sarilumab 200 mg group, and placebo group, respectively (primary outcome of the Phase 2 trial). At the time of data analysis, of the 226 critical patients, the proportion of patients who had died or were on a ventilator was lower in the sarilumab 400 mg group (28%) than in the sarilumab 200 mg group (46%) and in the placebo group (55%). Comparing mortality alone, the proportion of patients who died was also lower in the sarilumab 400 mg group (23%) than in the sarilumab 200 mg group (36%) and in the placebo group (27%). In contrast to the positive trend in outcomes among the patients with critical illness, the press release cited "negative trends" for most outcomes in patients with severe illness who received sarilumab.[41]
Siltuximab	• Multicentric Castleman disease	• Human-mouse chimeric monoclonal antibody • IL-6 antagonist[42]	**For COVID-19:** • *Not Peer Reviewed.* In a single-center observational study of 21 patients with COVID-19 who developed pneumonia/ARDS and received treatment with IV siltuximab, some patients experienced decreased CRP levels (16 of 21 patients) and improved clinical condition (7 of 21 patients) following siltuximab treatment. Other patients experienced no clinically relevant change in condition (9 of 21 patients) or worsening condition (5 of 21 patients). Among the 5 patients with worsening condition, there was 1 death and 1 cerebrovascular event (median follow-up of 8 days).[43]
Tocilizumab	• Cytokine release syndrome (induced by CAR T-cell therapy) • Rheumatoid arthritis • Giant cell arteritis • Polyarticular juvenile idiopathic arthritis • Systemic juvenile idiopathic arthritis[44]	• Recombinant humanized monoclonal antibody • IL-6 receptor antagonist	**For COVID-19:** • *Press Release:* Early results were reported for the CORIMUNO-TOCI trial (*ClinicalTrials.gov* Identifier NCT04331808), an open-label, randomized trial of hospitalized patients with COVID-19 (n = 129) at 7 sites in France. The patients, who had moderate or severe disease at study entry, were randomized to receive tocilizumab plus SOC (n = 65) or SOC alone (n = 64). The dosing strategy was tocilizumab 8 mg/kg on Day 1; if there was no response (i.e., no decrease of oxygen requirement), a second infusion was repeated on Day 3. In this preliminary report, the proportion of participants who died or needed ventilation (noninvasive or mechanical) was lower in the tocilizumab group than in the SOC alone group. Detailed results of the trial have not been reported. • 63 hospitalized adult patients were enrolled in a prospective open-label study of tocilizumab for severe COVID-19. All patients received off-label ARV PIs.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Interleukin-6 Inhibitors, continued			
Tocilizumab, continued			Patients received either tocilizumab IV (8 mg/kg) or SQ (324 mg); within 24 hours, a second dose was administered to 52 of the 63 patients. Following tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The PaO_2/FiO_2 ratio increased between admission (152 +/-53 mm Hg) and Day 7 (284 +/-116 mm Hg). No moderate or severe AEs attributable to tocilizumab were reported. Overall mortality was 11% (7 deaths among the 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association of reduced mortality with earlier use of tocilizumab, but provide no details regarding a comparison group or specify an a-priori comparison, which limits interpretation of this result.[45] • An uncontrolled, retrospective cohort study of 21 hospitalized COVID-19 patients who received tocilizumab reported improvement in oxygenation and systemic inflammation. At study entry, among the 21 patients (mean age 56 years; range 25 to 88 years), 17 had severe disease and 4 had critical disease. All patients were febrile, had abnormal chest CT findings, and required oxygen supplementation (2 required mechanical ventilation). Mean CRP level was 75 mg/L, mean IL-6 expression level was 153 pg/mL, mean D-dimer level was 0.80 g/mL, and mean lymphocyte percentage was 15.5%. Eighteen patients were given tocilizumab IV infusion once, and within 12 hours, 3 patients received a second infusion for indication of fever. Following tocilizumab administration, fevers normalized, lymphocyte percentages improved, and CRP levels declined. By Day 5, oxygen requirements were reduced in 15 of 20 participants (75%). There were no serious AEs attributed to tocilizumab, and no concurrent bacterial, fungal, or viral infections were observed during the treatment. The interpretability of this retrospective case series is limited due to its small sample size and lack of control group.[46] • Additional data supporting the use of tocilizumab for COVID-19 include a small retrospective cohort study, a case series, and a case-control study.[47-49]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Kinase Inhibitors: Bruton's Tyrosine Kinase Inhibitors			
Acalabrutinib	• Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) • Mantle cell lymphoma (MCL)[50]	• Second-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm[51]	**For COVID-19:** • Data regarding acalabrutinib are limited to a retrospective case series in 19 patients with severe COVID-19. However, data interpretation to discern any clinical benefit is limited by the study's small sample size and lack of a control group.[52]
Ibrutinib	• Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) • Mantle cell lymphoma (MCL) • Marginal zone lymphoma (MZL) • Waldenström macroglobulinemia (WM) • Chronic graft-versus-host disease (cGVHD) in stem cell transplant recipients[53]	• First-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm[54]	**For COVID-19:** • Data regarding ibrutinib are limited to an uncontrolled, retrospective case series of 6 patient with COVID-19 who were receiving ibrutinib for a condition other than COVID-19. However, evaluation of the data for any clinical benefit is limited by the study's small sample size and lack of control group.[54]
Zanubrutinib	• Mantle cell lymphoma (MCL)[55]	• Second-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm[51]	• No clinical data for COVID-19, SARS, or MERS

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Kinase Inhibitors: Janus Kinase Inhibitors			
Baricitinib	• Rheumatoid arthritis[56]	• JAK inhibitor selective for JAK1, JAK2, and TYK2, relative to JAK3 • Theoretical direct antiviral activity through inhibition of kinases (AAK1 and cyclin G-associated kinase) that regulate viral endocytosis in pulmonary AT2 epithelial cells, which may prevent SARS-CoV-2 entry into and infection of susceptible cells. • Dose-dependent inhibition of IL-6 induced STAT3 phosphorylation[57]	**For COVID-19:** • *Not Peer Reviewed.* A small, nonrandomized study of 12 patients with moderate COVID-19 pneumonia compared therapy with baricitinib and LPV/r with SOC alone (i.e., combination LPV/r and HCQ).[58] Baricitinib and LPV/r therapy demonstrated a statistically significant time to improvement in clinical and respiratory symptoms and reduction in measured CRP.[58]
Ruxolitinib	• Myelofibrosis • Polycythemia vera • Steroid-refractory acute graft-versus-host disease[59]	• JAK inhibitor selective for JAK1 and JAK2 • Theoretical antiviral properties through inhibition of AAK1 which may prevent viral entry into and infection of pulmonary AT2 alveolar epithelial cells[60,61] • Inhibition of IL-6 via JAK1/JAK2 pathway inhibition	**For COVID-19:** • A small, prospective, single-blind randomized controlled Phase 2 trial in patients with COVID-19 in China compared ruxolitinib 5 mg PO twice daily (n = 20) to placebo (vitamin C 100 mg; n = 21), both given in combination with SOC therapy. The median age of the patients was 63 years. There were no significant demographic differences between the two arms. Treatment with ruxolitinib was associated with a non-significant reduction in median time to clinical improvement (12 days for ruxolitinib vs. 15 days for placebo; $P = 0.15$), defined as a 2-point improvement on a 7-category ordinal scale or hospital discharge. There was no difference between the groups in the median time to discharge (17 days for ruxolitinib vs. 16 days for placebo; $P = 0.94$). More patients in the ruxolitinib group than in the placebo group had radiographic improvement on CT scans of the chest at Day 14 (90% for ruxolitinib vs. 61.9% for placebo; $P = 0.05$), and a shorter time to recovery from initial lymphopenia when present (5 days for ruxolitinib vs. 8 days for placebo; $P = 0.03$). The use of ruxolitinib was not associated with an increased risk of AEs or mortality (no deaths in the ruxolitinib group vs. 3 deaths [14% of patients] in the control group). Despite the theoretical antiviral properties of JAK inhibitors, there was no significant difference in time to viral clearance among patients who had detectable viral loads at randomization to ruxolitinib (n = 8) or placebo (n = 9). Limitations of this study include the small sample size, the exclusion of ventilated patients at study entry, and the frequent concomitant use (by 70% of patients) of antivirals and steroids.[62] • A small retrospective single-arm study in Germany reported no safety concerns in 14 patients with severe COVID-19 who received a brief course of ruxolitinib therapy (median 9 days).[63]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Kinase Inhibitors: Janus Kinase Inhibitors, continued			
Tofacitinib	• Rheumatoid arthritis • Psoriatic arthritis • Ulcerative colitis[64]	• JAK inhibitor selective for JAK1 and JAK3 with modest activity against JAK2 • Blocks signaling from gamma-chain cytokines (IL-2, IL-4) and gp 130 proteins (IL-6, IL-11, IFNs) • Shown to decrease levels of IL-6 in rheumatoid arthritis[65]	• No clinical data for COVID-19, SARS, or MERS

Key: AAK1 = Adaptor-associated kinase 1; ADE = antibody-dependent enhancement; AE = adverse event; ARDS = acute respiratory distress syndrome; ARV = antiretroviral; AT2 = alveolar type 2; AZM = azithromycin; BTK = Bruton's tyrosine kinase; CAR = chimeric antigen receptor; CRP = C-reactive protein; CI = confidence interval; CT = computerized tomography; EHR = electronic health record; EIND = Emergency Investigational New Drug Application; FDA = Food and Drug Administration; GAK = cyclin G-associated kinase; HCQ = hydroxychloroquine; HR = hazard ratio; HSR = hypersensitivity reaction; ICU = intensive care unit; IDMC = independent data monitoring committee; IFN = interferon; IL = interleukin; IND = Investigational New Drug application; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; JAK = Janus kinase inhibitor; MERS = Middle East respiratory syndrome; MERS-CoV = Middle East respiratory syndrome coronavirus; MSC = mesenchymal stem cells; NEWS2 = National Early Warning Score 2; OR = odds ratio; PCR = polymerase chain reaction; PI = protease inhibitor; RR = age-adjusted rate ratio; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SOFA = sequential organ failure assessment; SQ = subcutaneous; STAT3 = signal transducer and activator of transcription 3; TACO = transfusion-associated circulatory overload, TRALI = transfusion-related acute lung injury

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Table 3b. Characteristics of Immune-Based Therapy Under Evaluation for the Treatment of COVID-19

Last Updated: July 17, 2020

- The information in this table is derived from data on the use of these drugs and biologic products for FDA-approved indications or in investigational trials; it is supplemented with data on their use in patients with COVID-19 where available.
- The effective dosing of these agents for the treatment of COVID-19 is unknown. Therefore, the doses listed below are primarily derived from FDA-approved indications or from clinical trials investigating therapies for COVID-19.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- Treatment-related AEs associated with immune-based therapy in patients with COVID-19 are not well defined. Whether the frequency and severity of AEs associated with use of these agents for FDA approved-indications is the same in patients with COVID-19, especially in critically ill patients, is unknown. Reported AEs of these drugs that are associated with long-term therapy (i.e., months to years) are not included in this table because treatment for COVID-19 is not long term. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with treatment for COVID-19. When using concomitant medications with similar toxicity profiles, consider additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of combination therapies for treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA *Medwatch* program.
- For drug interaction information, please refer to product labeling and visit the Liverpool COVID-19 Drug Interactions website.
- For information on drugs that prolong the QTc interval, please visit CredibleMeds.org.

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood Products					
COVID-19 Convalescent Plasma	Single or multiple transfusions based on patient response	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • Red cell alloimmunization • Transmission of infectious pathogens[1] • Thrombotic events	• Monitor for transfusion-related reactions. • Vital signs at baseline and during and after transfusion.	Drug products **should not be added** to the IV infusion line for the blood product.	• There are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma or SARS-CoV-2 immunoglobulins for the treatment of COVID-19. • A list of clinical trials is available: Convalescent Plasma
Immunoglobulins: SARS-CoV-2 Specific	Varies by clinical trial	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • Red cell alloimmunization • Transmission of infectious pathogens	• Monitor for transfusion-related reactions. • Vital signs at baseline and during and after transfusion	Drug products **should not be added** to the IV infusion line for the blood product	• There are insufficient data for the Panel to recommend either for or against SARS-CoV-2 immunoglobulins for the treatment of COVID-19. • A list of clinical trials is available: Immunoglobulin

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Blood Products, continued					
Immunoglobulins: Non-SARS-CoV-2 Specific	Doses vary based on indication and formulation.	• Allergic reactions including anaphylaxis • Renal failure • Thrombotic events • Aseptic meningitis syndrome • Hemolysis • TRALI • Transmission of infectious pathogens	• Monitor for transfusion-related reactions. • Vital signs at baseline and during and after infusion • Discontinue if renal function deteriorates during treatment.	IVIG may interfere with immune response to certain vaccines.	• The Panel **recommends against** the use of non-SARS-CoV-2 specific IVIG for the treatment of COVID-19, except in a clinical trial **(AIII)**. This should not preclude the use of IVIG when otherwise indicated for treatment of complications that arise during COVID-19. • AEs may vary by formulation. • AEs may be precipitated by high dose, rapid infusion, or underlying conditions. • A list of clinical trials is available: Intravenous Immunoglobulin
Mesenchymal Stem Cells	Varies by clinical trial Mesenchymal stem cells should not be used in the United States for the treatment of COVID-19 outside of an FDA-approved clinical trial, expanded access protocol, or EIND process.	• Failure of the cells to work as expected[2] • Potential for mesenchymal stem cells to multiply or change into inappropriate cell types • Product contamination • Growth of tumors • Infections • Thrombus formation[3] • Administration site reactions[4,5]	• Monitor for administration site reactions.	Drug products should not be added to the IV infusion line for the MSC product.	• The Panel **recommends against** the use of mesenchymal stem cells for the treatment of COVID-19, except in a clinical trial **(AII)**. • The FDA has issued several warnings about patients being potentially vulnerable to stem cell treatments that are illegal and potentially harmful.[4] A number of cord blood-derived products are currently licensed by the FDA for various indications such as the treatment of cancer (stem cell transplant) and rare genetic diseases. These products are not FDA approved for the treatment of COVID-19. • A list of clinical trials is available: Mesenchymal Stem Cells

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Immunomodulators					
Corticosteroids					
Dexamethasone	**For COVID-19:** • Dexamethasone 6 mg daily IV or PO, for up to 10 days[6]	• Hyperglycemia • Secondary infections • Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) • Psychiatric disturbances • Adrenal insufficiency • Increased blood pressure • Peripheral edema • Myopathy (particularly if used with neuromuscular blocking agents) • In outbreaks of other novel coronavirus infections (i.e., MERS and SARS), corticosteroid therapy was associated with delayed virus clearance.[7,8]	• Blood glucose • Blood pressure • Sign and symptoms of new infection	• Moderate CYP3A4 inducer • CYP3A4 substrate • Minimal to no reduction in remdesivir exposure is expected with coadministration of dexamethasone (Gilead communication).	• The Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) for the treatment of COVID-19 in patients who are mechanically ventilated **(AI)** and in patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**. • The Panel **recommends against** using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**. • Currently, it is not known whether other corticosteroids (e.g., prednisone, methylprednisolone, or hydrocortisone) will provide a benefit like that with use of dexamethasone. The approximate daily doses equivalent to dexamethasone 6 mg daily for prednisone, methylprednisolone, and hydrocortisone are 40 mg, 32 mg, and 160 mg, respectively. • Remdesivir was not part of the treatment in the RECOVERY trial, therefore the safety and efficacy of remdesivir and dexamethasone used together are not known. • Dexamethasone is available as oral tablet, oral solution, oral elixir, and IV solution • A list of clinical trials is available: Dexamethasone

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons					
Interferon Alfa	• Peginterferon alfa-2a 180 mcg SQ once weekly for 2 weeks for MERS[9,10] **IFN Alfa-2b:** • *COVID-19 Clinical Trial Dosing:* Nebulized IFN alfa-2b 5 million units twice daily (no duration listed in the study)[11]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[12] • Injection site reactions • Liver function abnormalities • Decreased blood counts • Worsening depression • Insomnia • Irritability • Nausea • Vomiting • Hypertension • Induction of autoimmunity	• CBC with differential • Liver enzymes; avoid if Child-Pugh Score >6 • Depression, psychiatric symptoms • Reduce dose in patients with CrCl <30 mL/min.	• Low potential for drug interactions • Inhibition of CYP1A2	• The Panel **recommends against** the use of IFNs for the treatment of severely and critically ill COVID-19 patients, except in a clinical trial **(AIII)**. • For COVID-19, IFN-alfa has primarily been used as nebulization and usually as part of a combination regimen. • Nebulized IFN-alfa-2b is not approved in the United States. • IFN alfa-1b is not approved in the United States. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN; discontinue if accompanied by increase in bilirubin. • Reduce dose or discontinue if neutropenia or thrombocytopenia occur. • A list of clinical trials is available: Interferon

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons, continued					
Interferon Beta	**IFN Beta-1a:** • 44 mcg SQ three times weekly[10] for MERS • Duration for COVID-19 unknown **IFN Beta-1b:** • 8 million units SQ, every other day, up to 7 days total for COVID-19[13]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[14] • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity	• Liver enzymes • CBC with differential • Worsening CHF • Depression, suicidal ideation	Low potential for drug interactions	• The Panel **recommends against** the use of IFNs for the treatment of severely and critically ill COVID-19 patients, except in a clinical trial **(AIII)**. • There are insufficient data to recommend for or against the use of IFN-beta for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN. • A list of clinical trials is available: Interferon **Availability:** • Several products are available in the United States; product doses differ. *IFN Beta-1a Products:* • Avonex, Rebif *IFN Beta-1b Products:* • Betaseron, Extavia

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-1 Inhibitor					
Anakinra	• Standard adult dose is anakinra 100 mg SQ once daily • Has also been used IV • Duration unknown	• Neutropenia (particularly in combination with other agents that can cause neutropenia) • Anaphylaxis • Headache, nausea, diarrhea, sinusitis, arthralgia, flu-like symptoms, and abdominal pain • Injection site reactions • Liver enzyme elevations	• CBC with differential • Renal function (reduce dose in patients with CrCl <30 mL/min) • Liver enzymes	Use with TNF-blocking agents **is not recommended** due to increased risk of infection.	• There are insufficient data for the Panel to recommend either for or against the use of IL-1 inhibitors (e.g., anakinra) for the treatment of COVID-19. • A list of clinical trials is available: Anakinra
Interleukin-6 Inhibitors					
Sarilumab[15]	**Clinical Trial Dosing (See NCT04315298):** • Sarilumab 400 mg IV (single dose)[16] **Note:** The only FDA-approved sarilumab product is an SQ formulation.	• Neutropenia, thrombocytopenia • Gastrointestinal perforation • HSR • Increased liver enzymes • HBV reactivation • Infusion reaction possible	• Monitor for HSR • Monitor for infusion reaction • Neutrophils • Platelets • Liver enzymes	• Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• There are insufficient data for the Panel to recommend for or against the use of sarilumab for the treatment of COVID-19. • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • A list of clinical trials is available: Sarilumab

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-6 Inhibitors, continued					
Siltuximab	• Siltuximab 11 mg/kg IV over 1 hour every 3 weeks for multicentric Castleman disease[17] • Dose and duration for COVID-19 unknown	• Infusion-related reaction • HSR • Gastrointestinal perforation • Neutropenia • Hypertension • Dizziness • Rash • Pruritus • Hyperuricemia	• Monitor for HSR • Monitor for infusion reaction • Neutrophils	• Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• There are insufficient data for the Panel to recommend for or against the use of siltuximab for the treatment of COVID-19. • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • A list of clinical trials is available: Siltuximab
Tocilizumab[18]	**Clinical Trial Dosing:** • Tocilizumab 8 mg/kg IV once • Dose **should not exceed** tocilizumab 800 mg. • Dose may be repeated once, 12 hours later, if clinical symptoms worsen or show no improvement (see NCT04320615).	• Infusion-related reactions • HSR • Gastrointestinal perforation • Hepatotoxicity • Treatment-related changes in neutrophils, platelets, lipids, and liver enzymes • HBV reactivation	• Monitor for HSR • Monitor for infusion reactions • Neutrophils • Platelets • Liver enzymes	• Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• There are insufficient data for the Panel to recommend either for or against the use of tocilizumab for the treatment of COVID-19. • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • SQ formulation **is not intended** for IV administration. • A list of clinical trials is available: Tocilizumab

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Kinase Inhibitors					
Bruton's Tyrosine Kinase Inhibitors					
Acalabrutinib	**Dose for FDA-Approved Indications:** • Acalabrutinib 100 mg PO every 12 hours • Dose and duration for COVID-19 unknown	• Hemorrhage • Cytopenias (neutropenia, anemia, thrombocytopenia, lymphopenia) • Atrial fibrillation and flutter • Infection • Headache • Diarrhea • Fatigue • Myalgia	• CBC with differential • Signs and symptoms of bleeding (particularly if coadministered with anticoagulant or antiplatelet therapy) • Clinical monitoring for cardiac arrhythmias • Monitor for new infections	• Avoid concomitant use with strong CYP3A inhibitors or inducers. • Dose reduction may be necessary with moderate CYP3A4 inhibitors. • Avoid concomitant PPI use. • H2-receptor antagonist should be administered 2 hours after acalabrutinib.	• The Panel **recommends against** the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Avoid in patients with severe hepatic impairment. • Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to atrial fibrillation. • A list of clinical trials is available: Acalabrutinib
Ibrutinib	**Doses for FDA-Approved Indications:** • Ibrutinib 420 mg or 560 mg PO once daily • Dose and duration for COVID-19 unknown	• Hemorrhage • Cardiac arrhythmias • Serious infections • Cytopenias (thrombocytopenia, neutropenia, anemia) • Hypertension • Diarrhea • Musculoskeletal pain • Rash	• CBC with differential • Blood pressure • Signs and symptoms of bleeding (particularly if coadministered with anticoagulant or antiplatelet therapy) • Clinical monitoring for cardiac arrhythmias • Monitor for new infections	• Avoid concomitant use with strong CYP3A inhibitors or inducers. • Dose reduction may be necessary with moderate CYP3A4 inhibitors.	• The Panel **recommends against** the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Avoid in patients with severe baseline hepatic impairment. Dose modifications required in patients with mild or moderate hepatic impairment. • Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to cardiac arrhythmias. • A list of clinical trials is available: Ibrutinib

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Bruton's Tyrosine Kinase Inhibitors, continued					
Zanubrutinib	**Dose for FDA-Approved Indications:** • Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily • Dose and duration for COVID-19 unknown	• Hemorrhage • Cytopenias (neutropenia, thrombocytopenia, anemia, leukopenia) • Atrial fibrillation and flutter • Infection • Rash • Bruising • Diarrhea • Cough • Musculoskeletal pain	• CBC with differential • Signs and symptoms of bleeding • Clinical monitoring for cardiac arrhythmias • Monitor for new infections	• Avoid concomitant use with moderate or strong CYP3A inducers. • Dose reduction required with moderate and strong CYP3A4 inhibitors.	• The Panel **recommends against** the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Dose reduction required for severe hepatic impairment. • A list of clinical trials is available: Zanubrutinib
Janus Kinase Inhibitors					
Baricitinib[19]	**For Rheumatoid Arthritis:** • Baricitinib 2 mg PO once daily **Doses for COVID-19 in Clinical Trials:** • Baricitinib 2 mg to 4 mg PO once daily for 7 to14 days	• Lymphoma and other malignancies • Thrombosis • Gastrointestinal perforation • Treatment-related changes in lymphocytes, neutrophils, hemoglobin, liver enzymes • Herpes simplex • Herpes zoster	• CBC with differential • Renal function • Liver enzymes • Monitor for new infections	Dose modification is recommended when concurrently administering with a strong OAT3 inhibitor.	• The Panel **recommends against** the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Baricitinib **is not recommended** in patients with severe hepatic or renal impairment. • A list of clinical trials is available: Baricitinib

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Janus Kinase Inhibitors, continued					
Ruxolitinib	• Doses for FDA-approved indications range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily. • Doses in COVID-19 clinical trials range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily, for 14 days.	• Thrombocytopenia • Anemia • Neutropenia • Liver enzyme elevations • Risk of infection • Dizziness • Headache • Diarrhea • CPK elevation • Herpes zoster	• CBC with differential • Liver enzymes • Monitor for new infections	• Dose modifications required when administered with strong CYP3A4 inhibitors. • Avoid use with fluconazole doses >200 mg.	• The Panel **recommends against** the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Dose modification may be required for moderate and severe renal impairment, hepatic impairment, and thrombocytopenia. • A list of clinical trials is available: Ruxolitinib
Tofacitinib	**Doses for FDA-Approved Indications:** • Tofacitinib 5 mg PO twice daily (rheumatoid and psoriatic arthritis) • Tofacitinib 10 mg PO twice daily (ulcerative colitis) • Dose and duration for COVID-19 unknown; A planned COVID-19 clinical trial will be evaluating 10 mg twice daily for 14 days	• Thrombotic events (pulmonary embolism, DVT, arterial thrombosis) • Anemia • Risk of infection • Gastrointestinal perforation • Diarrhea • Headache • Herpes zoster reactivation • Lipid elevations • Liver enzyme elevations • Lymphoma and other malignancies	• CBC with differential • Liver enzymes • Monitor for new infections	• Dose modifications required when administered with strong CYP3A4 inhibitors, or when used with a moderate CYP3A4 inhibitor coadministered with a strong CYP2C19 inhibitor. • Avoid live vaccines.	• The Panel **recommends against** the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Avoid use in patients with ALC <500 cells/mm^3, ANC <1000 cells/mm^3, or Hgb <9 grams/dL. • Dose modification may be required for moderate and severe renal impairment and moderate hepatic impairment. • A list of clinical trials is available: Tofacitinib

Key: AE = adverse effect or adverse event; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BTK = Bruton's tyrosine kinase; CBC = complete blood count; CHF = congestive heart failure; CrCl = creatinine clearance; CPK = creatine phosphokinase; CRP = C-reactive protein; CYP = cytochrome P; DVT = deep vein thrombosis; EIND = Emergency Investigational New Drug; FDA = Food and Drug Administration; HBV = hepatitis B; Hgb = hemoglobin; HSR = hypersensitivity reaction; HSV = herpes simplex virus; IFN = interferon; IL-1 = interleukin-1; IL-6 = interleukin-6; IV = intravenous; IVIG = intravenous immunoglobulin; JAK = Janus kinase; MERS = Middle East respiratory syndrome; OAT = organic anion transporter; PO = orally; PPI = proton pump inhibitor; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SQ = subcutaneous; TACO = transfusion-associated circulatory overload; TB = tuberculosis; the Panel = the COVID-19 Treatment Guidelines Panel; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

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